Important Prescribing Information

Subject: Temporary importation of Potassium Chloride (KCl) Injection, Concentrate, 2 mEq/mL to address drug shortage issues

July 11, 2018

Dear Healthcare Professional,

Due to the current critical shortage of Potassium Chloride for Injection, Concentrate, 2 mEq/mL in the United States (US) market, Athenex Pharmaceutical Division, LLC (Athenex) is coordinating with the U.S. Food and Drug Administration (FDA) to increase the availability of Potassium Chloride Injection Concentrate. Athenex has initiated temporary importation of another manufacturer's Potassium Chloride Injection Concentrate 2 mEq/mL into the U.S. market. This product is manufactured and marketed in Italy by Industria Farmaceutica Galenica Senese S.r.l. (Galenica).

Given the scale of this shortage, FDA is coordinating with several firms to import Potassium Chloride Injection 2 mEq/mL. At this time, however, no other entity except Athenex Pharmaceutical Division, LLC is authorized by the FDA to import or distribute Galenica's Potassium Chloride Injection Concentrate 2 mEq/mL ampule. FDA has not approved Galenica's Potassium Chloride Injection Concentrate 2 mEq/mL ampule but does not object to its importation into the United States. You may be provided with additional letters for other imported products you receive. Please read each letter in its entirety because each letter may contain different, product-specific information.

Effective immediately, and during this temporary period, Athenex will offer the following presentation of Potassium Chloride Injection Concentrate:

Product name and description	Size	Pack factor	NDC Number
Potassium Chloride Injection, Concentrate, 2 mEq/mL	10 mL	10 ampules per carton	72439-500-10

It is important to note the following:

- Each ampule contains potassium chloride 20 mEq/10 mL (2 mEq/mL). An image of the carton label is included in Table 1.
- Follow standard aseptic technique and withdraw contents of the ampule with a 5-micron filter needle. Change the needle before diluting in a solution for intravenous infusion.
- There is no barcode on the ampule or carton. Alternative procedures should be followed to assure that the correct drug product is being used.

A side by side comparison of the Hospira PI and the Galencia patient leaflet is included in the Table 2 at the end of this letter.

Please refer to the package insert for the FDA-approved Potassium Chloride for Injection Concentrate, USP drug product for full prescribing information.
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=559a0a8c-a8fe-40a5-b196-21f9308780ab&audience=consumer

To order or if you have questions about Galenica's KCl Injection 2 mEq/mL, 10 mL ampules, please contact Athenex's Customer Service by phone at 1-855-273-0154. Order number: AA0681002

To report adverse events among patients who have received Galenica's KCl Injection, 2 mEq/mL, 10 mL ampules, please contact Athenex's Medical Affairs by phone at 1-855-273-0154. Adverse events may also be reported to FDA's MedWatch Adverse Reporting Program either online, by regular mail or fax:

- Complete and submit the report **Online**: www.fda.gov/medwatch/report.htm
- **Regular Mail or Fax**: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178 (1-800-332-0178)

If you have any questions about the information contained in this letter or use of Galenica's KCl Injection 2 mEq/mL 10 mL ampules, please contact Athenex's Medical Affairs at 1-855-273-0154.

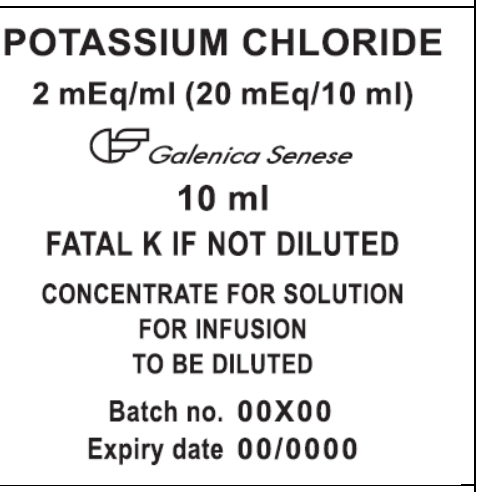
Sincerely,

Thomas J. Moutvic
Vice President, Regulatory Affairs
Athenex Pharmaceutical Division, LLC

TABLE 1

Principal Display Panel of Carton Labeling

TABLE 2
Product Comparison Table

	US Approved Product Hospira	Imported Product Galenica
Product name	**Potassium Chloride** for Injection **Concentrate**, USP	Potassium Chloride 2 mEq/mL concentrate for solution for infusion
Image of Container Label		
Active Ingredient	Potassium Chloride (parenteral fluid and electrolyte replenisher)	Potassium Chloride (electrolytic solution)
Available Strengths / Concentrations	10 mEq/5 mL (2 mEq/mL) 30 mEq/15 mL (2 mEq/mL) 20 mEq/10 mL (2 mEq/mL) 40 mEq/20 mL (2 mEq/mL)	2 mEq/mL (10 mL solution) - each mL contains 2 mEq of K+ and Cl-
Route of administration	For Intravenous Infusion after dilution	For Intravenous Infusion after dilution
Dosage	Infusion Solution	Infusion Solution
pH	4.6 (4.0 to 8.0)	5.5 to 6.5
excipients for pH adjustment	water for injection as needed and may contain hydrochloric acid for pH adjustment	water for injection as needed
Indications and Usage	Potassium Chloride for Injection Concentrate, USP is indicated in the treatment of potassium deficiency states when oral replacement is not feasible.	Treatment of potassium deficiency in patients for whom oral reintegration is not possible.
Contraindications	Potassium Chloride for Injection Concentrate, USP is contraindicated in diseases where high potassium levels may be encountered, and in patients with hyperkalemia, renal failure and in conditions in which potassium retention is present.	Hypersensitivity to the active substance or to any of the excipients; - hyperkalemia or in cases of potassium retention - severe renal impairment - untreated Addison's disease - acute dehydration - heat cramps
Warnings	To avoid potassium intoxication, do not infuse solutions rapidly. In patients with severe renal insufficiency, administration of potassium chloride may cause potassium intoxication and life-threatening hyperkalemia.	The solution must be clear, colorless and free of visible particles. Use immediately after opening the container. The container serves for one and continuous administration and any residue cannot be used.

	US Approved Product Hospira	Imported Product Galenica
Warnings (Cont'd)	The administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentration. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentration. WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.	**Pregnancy and lactation** **Ask your doctor or pharmacist for advice before taking any medicine.** No data are available on possible adverse effects of the medicinal product when administered during pregnancy or lactation or on reproductive capacity. Therefore, the medicinal product should not be used during pregnancy and lactation, unless absolutely necessary and only after a risk-benefit assessment has been carried out. **Effects on ability to drive and use machines** The medicinal product does not impair the ability to drive or use machinery.
Precautions	**General** Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements, or the use of electrolyte-free dextrose solutions to which individualized electrolyte supplements may be added.	High plasma concentrations of potassium can cause death from cardiac depression, arrhythmias or arrest. To avoid potassium poisoning, infusion should be slow. Administration should be guided through serrated electrocardiograms; potassiemia is not indicative of cellular potassium concentrations. It is good practice to monitor fluid balance, electrolytes and acid-base balance during infusion.

	US Approved Product Hospira	Imported Product Galenica
Precautions (Cont'd)	Potassium therapy should be guided primarily by serial electrocardiograms, especially in patients receiving digitalis. Serum potassium levels are not necessarily indicative of tissue potassium levels. Solutions containing potassium should be used with caution in the presence of cardiac disease, particularly in the presence of renal disease, and in such instances, cardiac monitoring is recommended. Solutions containing dextrose should be used with caution in patients with overt or known subclinical diabetes mellitus, or carbohydrate intolerance for any reason. If the administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result. **Pregnancy** *Teratogenic Effects*: Pregnancy category C. Animal reproduction studies have not been conducted with potassium chloride. It is also not known whether potassium chloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Potassium chloride should be given to a pregnant woman only if clearly needed.	The medicine should be administered with caution to patients: - with renal failure (administration of solutions containing potassium ions in patients with decreased renal function may cause potassium retention); - with heart failure, especially if digitized; - with adrenal insufficiency; - with liver failure; - with periodic family paralysis; - with congenital myotonia; - in the early post-operative phases.
Adverse Reactions	Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation, hypervolemia, and hyperkalemia. Too rapid infusion of hypertonic solutions may cause local pain and, rarely, vein irritation. Rate of administration should be adjusted according to tolerance.	Like all medicines, Potassium Chloride can cause side effects although not everyone gets them. The following are the side effects of Potassium Chloride. There are insufficient data available to determine the frequency of the individual listed effects. *Gastrointestinal disorders* Gastrointestinal disorders.

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Adverse Reactions (Cont'd)	Reactions reported with the use of potassium-containing solutions include nausea, vomiting, abdominal pain and diarrhea. The signs and symptoms of potassium intoxication include paresthesias of the extremities, areflexia, muscular or respiratory paralysis, mental confusion, weakness, hypotension, cardiac arrhythmias, heart block, electrocardiographic abnormalities and cardiac arrest. Potassium deficits result in disruption of neuromuscular function, and intestinal ileus and dilatation. If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.	*Nervous system disorders* Neuromuscular disorders, paresthesias, flaccid paralysis, weakness, mental confusion. *Cardiac diseases* Hypotension, arrhythmias, conduction disturbances, disappearance of the P wave, enlargement of the QRS in the electrocardiographic trace, cardiac arrest. *Disorders of the water and electrolytic balance* Hypervolemia. **Systemic disorders and conditions related to the site of administration** Febrile responses, infections in the injection site, venous or phlebitis thrombosis, extravasation. *Adherence to the instructions in the package insert reduces the risk of side effects.* *If any of the side effects get serious, or if you notice any side effects not listed in this package leaflet, please tell your doctor or pharmacist.*
Over dosage	In the event of fluid overload during parenteral therapy, re-evaluate the patient's condition, and institute appropriate corrective treatment. In the event of over dosage with potassium-containing solutions, discontinue the infusion immediately, and institute corrective therapy to reduce serum potassium levels. Treatment of hyperkalemia includes the following: 1. Dextrose Injection USP, 10% or 25%, containing 10 units of crystalline insulin per 20 grams of dextrose administered intravenously, at a rate of 300 to 500 mL per hour.	In case of overdose, immediately suspend infusion of the solution containing potassium and institute corrective therapy to reduce elevated plasma potassium levels and restore, if necessary, the acid-base balance (see Precautions for Use). In case of accidental ingestion/undertake of an excessive dose of Potassium Chloride inform your doctor immediately or contact the nearest hospital.

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Over dosage (Cont'd)	2. Absorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema. 3. Hemodialysis and peritoneal dialysis. The use of potassium-containing foods or medications must be eliminated. However, in cases of digitalization, too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.	If you are in any doubt about the use of Potassium Chloride, ask your doctor or pharmacist.
Dosage and Administration	Potassium Chloride for Injection Concentrate, USP must be diluted before administration. Care must be taken to ensure there is complete mixing of the potassium chloride with the large volume fluid, particularly if soft or bag type containers are used. The dose and rate of administration are dependent upon the specific condition of each patient. Dextrose Injection USP, 10% or 25%, containing 10 units of crystalline insulin per 20 grams of dextrose administered intravenously, at a rate of 300 to 500 mL per hour. Absorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema. Hemodialysis and peritoneal dialysis. The use of potassium-containing foods or medications must be eliminated. However, in cases of digitalization, too rapid a lowering of plasma potassium concentration can cause digitalis toxicity. If the serum potassium level is greater than 2.5 mEq/liter, potassium can be given at a rate not to exceed 10 mEq/hour in a concentration of up to 40 mEq/liter. The 24-hour total dose should not exceed 200 mEq.	The medicinal product shall not be injected as such. Fatal if swallowed undiluted (see Precautions for Use). The medicinal product should be administered intravenously only after dilution in 5% glucose solution or 0.9% sodium chloride solution (saline solution) or other compatible solutions (see end of this section). **Shake well during dilution preparation and before administration.** The dose depends on the age, weight and clinical condition of the patient, taking into account that the normal daily requirement of potassium is as follows Adults: 40-80 mEq per day. The total dose shall not exceed 200 mEq per day. Children: 2-3 mEq/kg per day. In children the safety and efficacy of potassium chloride have not been determined. The medicine should only be administered with intact renal function and at a rate not exceeding 10 mEq potassium/hour. Under emergency conditions (potassium values less than or equal to 2 mEq/l with electrocardiographic modifications and muscular paralysis) do not exceed the infusion rate of 40 mEq/hour, under electrocardiographic monitoring and do not exceed the dose of 400 mEq in 24 hours.

Dosage and Administration (Continued)	If urgent treatment is indicated (serum potassium level less than 2.0 mEq/liter with electrocardiographic changes and/or muscle paralysis) potassium chloride may be infused very cautiously at a rate of up to 40 mEq/hour. In such cases, continuous cardiac monitoring is essential. As much as 400 mEq may be administered in a 24-hour period. In critical conditions, potassium chloride may be administered in saline (unless contraindicated), rather than in dextrose containing fluids, as dextrose may lower serum potassium levels. Prior to entering vial, remove the metal seal and cleanse the rubber closure with a suitable antiseptic agent. Parenteral drug products should be inspected visually for particulate matter and discoloration, whenever solution and container permit. TO PREVENT NEEDLE-STICK INJURIES, NEEDLES SHOULD NOT BE RECAPPED, PURPOSELY BENT, OR BROKEN BY HAND.	Infusions that are too rapid can cause local pain and the infusion rate must be adjusted for tolerance. <u>Solutions to be used for the dilution of potassium chloride</u> See dose, manner, and time of administration. Dilute the solution immediately after opening the container; the diluted solution must be used immediately. It must be clear, colorless and free of visible particles. It serves for a single and uninterrupted administration and any residue cannot be used. Shake well during dilution preparation and before administration. Do not use if the solution is not clear, colorless, or contains particles. All usual precautions should be taken to maintain sterility before and during intravenous infusion.
Storage	Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]	<u>Deadline</u>: See expiration date on package. The expiry date refers to the product in intact packaging, correctly stored. **Warning**: Do not use the medicine after the expiry date shown on the packaging. <u>Storage conditions</u> Store in the original container and in the hermetically sealed container. Do not refrigerate or freeze. Medicines must not be disposed of in waste water or household waste. Ask your pharmacist how to dispose of medicines that you no longer use. This will help to protect the environment. **Keep the medicine out of the reach and sight of children.**

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Additional Sections:		
Clinical Pharmacology	Potassium is the chief cation of body cells (160 mEq/liter of intracellular water) and is concerned with the maintenance of body fluid composition and electrolyte balance. Potassium participates in carbohydrate utilization and protein synthesis and is critical in the regulation of nerve conduction and muscle contraction, particularly in the heart. Chloride, the major extracellular anion, closely follows the metabolism of sodium, and changes in the acid-base balance of the body are reflected by changes in the chloride concentration. Normally about 80 to 90% of the potassium intake is excreted in the urine, the remainder in the stools and, to a small extent, in perspiration. The kidney does not conserve potassium well so that during fasting, or in patients on a potassium-free diet, potassium loss from the body continues, resulting in potassium depletion. A deficiency of either potassium or chloride will lead to a deficit of the other.	Section not in Galenica PI
Interactions	Section not in Pfizer PI	**Inform your doctor or pharmacist if you have recently taken any other medicines, including medicines obtained without a prescription.** The use of drugs such as potassium-sparing diuretics may increase the risk of hyperkalemia, particularly in the presence of renal dysfunction. Therefore, serum potassium levels should be closely monitored in such cases. The use of drugs such as ACE inhibitors that cause aldosterone levels to decrease, may lead to potassium retention. Therefore, serum potassium levels should be closely monitored.

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